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COOPERATIVE STUDIES

Prognostic Significance of Ventricular Ectopic Activity in Survivors of Acute Myocardial Infarction

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Twenty-four hour ambulatory electrocardiography was performed on 3,290 survivors of acute myocardial infarction participating in the Beta-Blocker Heart Attack Trial (BHAT). History of myocardial infarction before the qualifying event, congestive heart failure and age were independently associated with the frequency and complexity of ventricular premature beats. Of the 1,640 patients randomized to placebo therapy, 163 died (76 suffered sudden death) during a 25 month average follow-up period. Ventricular ectopic activity was an independent predictor of total mortality after taking into consideration 16 other prognostic factors describing past history, risk factors, physical examination and laboratory investigations.

Seven categoric definitions of ventricular ectopic activity predicted mortality, with similar odds ratios ranging from 2.27 to 2.69. A reciprocal relation of the sensitivity and specificity of each definition in predicting mortality was observed. Three clinical criteria (ST depression, cardiomegaly and prior infarction) allowed stratification of patients into four subsets with respective mortality rates of 35.5% (three criteria present), 19.0% (two criteria), 11.5% (one criterion) and 4.7% (none). Presence of ventricular ectopic activity (≥10 ventricular premature beats/h or pairs, ventricular tachycardia or multiform complexes) was associated with higher mortality rates in all four risk strata. The relative risk was higher (3.86) in the lowest risk stratum (mortality 2.4% without and 9.1% with ventricular ectopic activity).

Thus, in survivors of acute myocardial infarction, ventricular ectopic activity was more pronounced in patients with prior myocardial infarction and congestive heart failure. It predicted mortality independently of other factors. Although mortality ratios were similar for all seven arrhythmia definitions, a reciprocal relation between sensitivity and specificity of the definitions in predicting mortality existed; ventricular ectopic activity was associated with increased mortality in all risk strata, but with a higher risk ratio in the numerically larger, low risk subset.

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A relation between ventricular ectopic activity recorded 1 to 3 weeks after an acute myocardial infarction and future mortality has been reported (1–36). Although this relation may be explained by the association of ectopic activity with other factors aggravating prognosis (for example, the degree of left ventricular dysfunction), many studies (15,16,19,24,25,29,30,32,33,35) suggest that ventricular arrhythmia contributes to the risk independently of other prognostic factors.

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Additional data on the prognostic value of ventricular ectopic activity are desirable because the relative usefulness of various definitions of ectopic activity has not been assessed accurately, the contribution of ambulatory electrocardiography (ECG) in determining the risk of mortality in different subsets of survivors of myocardial infarction is not known and there are only a few studies with a large number of patients studied by 24 hour ambulatory ECG. To answer these questions, the Beta Blocker Heart Attack Trial (BHAT) allowed the collection of data on a large number of patients from a wide geographic distribution. This report pertains to 1,640 patients with a recent myocardial infarction who were randomized into the BHAT placebo group and who had a 24 hour ambulatory ECG at baseline study.

The objectives of this report are 1) to define the usefulness of various definitions of ventricular ectopic activity in predicting the mortality rate among survivors of acute myocardial infarction; 2) to describe a simple risk classification system based on easily obtained clinical variables; and 3)

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to define the value of ambulatory ECG in determining risk in patient subsets with a high or low risk for mortality. In addition, the association of ventricular ectopic activity with other clinical variables and its independent association with future mortality are described.

Methods

Population and variables studied. The BHAT was a multicenter randomized placebo-controlled double-blind clinical trial with the primary objective of testing the effect of long-term administration of propranolol on mortality in patients who had survived an acute myocardial infarction. The design and baseline findings of the trial have been reported elsewhere (37). The effect of propranolol on mortality (that is, a significant decrease in total mortality, atherosclerotic heart disease mortality and sudden cardiac death [<1 hour]) has also been reported (38). The data presented here pertain to 1,640 patients randomized to the placebo group who had 24 hour ambulatory ECG 2 to 21 days after admission to a coronary care unit. There was no correlation between ventricular ectopic activity and the number of days since the qualifying infarction ($r = 0.059$). Analyses of the relation of the time interval between qualifying infarction and ambulatory ECG with mortality were inconclusive because of the small number of deaths in some subsets. The patients who did and did not have 24 hour ambulatory ECG were not different in demographic and clinical characteristics.

Patients with a definite acute myocardial infarction diagnosed by predetermined criteria (typical symptoms and specified changes in cardiac enzymes and the ECG) were enrolled by 31 clinical centers (134 hospitals). Patients with a history of severe congestive heart failure, bronchial asthma as an adult, marked bradycardia and life-threatening illness other than coronary artery disease, those who had or were likely to have aortocoronary bypass surgery and those who were taking or were likely to take a beta-adrenergic blocking agent were excluded. During approximately 2 years of enrollment, 3,837 patients were randomized (1,916 to propranolol therapy and 1921 to placebo therapy).

History, physical examination, 12 lead ECG, cardiac enzymes, hematocrit, complete blood count and biochemical determinations were obtained from all patients before randomization. In addition, 24 hour ambulatory ECG was performed in 3,290 patients (86% of all patients). In approximately 15% of the patients, ambulatory ECG could not be done before randomization because of equipment and personnel constraints and other administrative reasons. Two channel, reel to reel ECG recordings were obtained using portable tape recorders (Avionics model 445). They were processed by a central laboratory (CardioData) using the Worcester Polytechnic Institute Algorithm. This validated computer-operator interactive system is able to differentiate up to 25 different ECG rate and rhythm variables (39,40). A quality control program of blind analysis of previously hand-counted tapes and blind reanalysis of 4% of the BHAT tapes was used. Acceptable deviations in this quality control procedure were a mean monthly error of <7% in ventricular ectopic activity counts compared with hand-counted tapes and a maximal error in any given sample of less than 14%.

Follow-up. Follow-up visits were made 1 month and 6 weeks after randomization and every 3 months thereafter for the duration of the study. Deaths during the mean 25 month follow-up period (range 12 to 40 months) were classified by a subcommittee of investigators unaware of the treatment group assignment or the results of ambulatory ECG. This group considered death certificates, attending physician reports, hospital records, autopsy reports and information obtained from relatives and witnesses.

Data analysis. This report will first present the baseline correlates of ventricular ectopic activity. Analysis of the relation of ectopic activity to baseline variables was based on the 3,290 patients who had ambulatory ECG before randomization. Analyses evaluating the relation between ectopic activity and follow-up events are restricted to the 1,640 placebo-treated patients who underwent 24 hour baseline ambulatory ECG monitoring (85% of all placebo-treated patients).

Among 40 baseline characteristics describing past medical history (for example, angina, myocardial infarction), risk factors, life style (for example, employment, exercise), physical examination and laboratory determinations, 11 to 16 were used as independent covariates in multivariate logistic regression models describing the contribution of different definitions of ventricular ectopic activity in predicting cause-specific mortality. These variables (listed in the Appendix) were selected from previous multivariate analyses as the variables that best predicted cause-specific mortality in the BHAT placebo-treated group of patients.

In addition, patients were stratified according to the presence or absence of three clinical characteristics (history of prior myocardial infarction, cardiomegaly on chest X-ray study defined by a cardiothoracic ratio >0.50 and ST depression on the rest ECG). These characteristics were chosen because of their strong association with mortality in this and previous studies and because they are easily obtained during routine care of patients. In this study, these criteria had the third, fifth and sixth strongest association with mortality (after age, ventricular ectopic activity and congestive heart failure).

Eleven definitions were used to describe ventricular ectopic activity. Four definitions are continuous [average number of ventricular premature beats (VPB)/h: ln (VPB/h + 0.5); VPB pairs/h; episodes of ventricular tachycardia (≥3 consecutive beats)/h], while seven are categoric [mean VPBs/h >0; mean VPBs/h ≥10; presence of ventricular tachycardia event or pairs; mean VPBs/h ≥10 or ventricular tachycardia

Table 1. 24 Hour Ambulatory Electrocardographic (Holter) Characteristics of the BHAT Placebo Group at Baseline Study

Holter Characteristic	Overall (n = 1,640)	Patients not Receiving Antiarrhythmic Drugs at Entry (n = 1,349)
VPB/h (arithmetic mean)	13.5	10.3
VPB/h (median)	0.298	0.276
VPB/h (mode)	0.0	0.0
VPB/h (geometric mean)*	1.1	0.9
VPB pairs/h (mean)	0.235	0.184
VT events/h (mean)	0.020	0.018
Mean VPB/h >0 (%)	84.1	83.2
Mean VPB/h ≥10 (%)	12.9	10.6
VT event or VPB pairs present (%)	19.9	19.0
VPB ≥10/h or (VT event or pairs) (%)	25.5	23.6
Multiform VPB present (%)	32.8	30.9
VPB ≥10/h and (VT event or pairs) and multiform complexes (%)	6.8	5.6
VPB ≥10/h or (VT event or pairs) or multiform complexes (%)	40.6	38.5

*Geometric mean ≅ [exp(Σ ln(VPB + 0.5)/n) − 0.5]. VPB = ventricular premature beat; VT = ventricular tachycardia.

event or pairs; presence of multiform VPBs; VPBs/h ≥10 and (ventricular tachycardia event or pair) *and* multiform; VPB/h ≥10 or (ventricular tachycardia event or pair) *or* multiform]. Because of the problem of multiple comparisons and because many baseline characteristics and many end points are intercorrelated, probability (p) values are not presented in this report. Student's *t* test values and odds ratios will be presented as guides to the magnitude of the associations. Traditionally, *t* values >1.96 are considered significant.

Results

Prevalence and correlates of ventricular ectopic activity at baseline (Tables 1 and 2). Table 1 shows the characteristics of ventricular ectopic activity of the 1,640 patients with acute myocardial infarction recorded in the BHAT placebo group. Eighty-four percent of the patients had at least one ventricular premature beat/24 h, approximately 20% had repetitive forms, approximately 13% had an average of ≥10 ventricular premature beats/h and approximately 33% had multiform complexes. Similar values pertained when the 291 patients who were receiving antiarrhythmic agents during ambulatory ECG were excluded from the analysis. Also, analysis of the total cohort of 3,290 patients studied at baseline yielded similar results (arithmetic mean 13.3 VPB/h, median 0.29 VPB/h, mode 0 VPB/h, patients with more than 0 VPB/h, 83.4%).

Multivariate linear regression analyses (Table 2) performed for the 3,225 patients in the BHAT trial who had a complete set of baseline data using 11 independent variables found to be univariately associated with ventricular arrhythmia or hypothesized to be so related, showed significant independent relations between ventricular ectopic activity and the following three factors: history of a myocardial

Table 2. Multivariate Relation Between Ventricular Arrhythmias and 11 Baseline Variables: Multiple Linear Regression in 3,225 Patients

Independent Baseline Variables	Dependent Variable = ln (VPB/h + 0.5)		Dependent Variable = Presence* of ≥10 VPB/h		Dependent Variable = Presence* of "Complex" VPB	
	Adjusted *t* Values	Coefficient	Adjusted *t* Values	Coefficient	*t* Values	Coefficient
Prior MI*	10.57	0.82	8.09	0.14	7.28	0.18
Age (yr)	7.83	0.026	4.99	0.004	7.06	0.008
Congestive heart failure*	3.76	0.28	3.30	0.06	2.98	0.07
Rose questionnaire angina in past year*	2.37	0.20	2.09	0.04	0.78	0.02
Race (0 = black; 1 = white/other)	−2.03	−0.19	−1.58	−0.03	−1.41	−0.04
Systolic blood pressure (mm Hg)	1.70	0.0040	1.44	0.0008	2.19	0.002
Atrial fibrillation*	1.26	0.14	1.07	0.27	1.93	0.07
ST depression*	0.95	0.06	−0.39	−0.005	1.94	0.04
Heart rate (beats/min)	0.60	0.002	0.64	0.0004	−0.27	−0.0002
Current smoker*	0.50	0.03	−0.25	−0.003	0.16	0.003
Serum potassium (mEq/liter)	0.17	0.15	0.70	0.13	0.21	0.06
Intercept	—	−1.74	—	−0.32	—	−0.26

*0 = no, 1 = yes; "Complex" VPB = ≥10 VPB/h or run or multiform complex. Abbreviations as before.

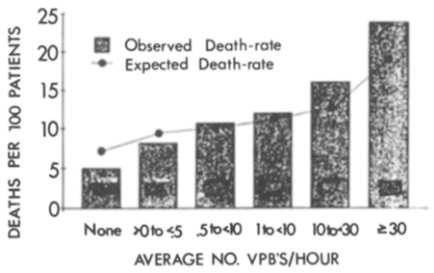

Figure 1. Relation between mortality rate and increasing number of ventricular premature beats (VPBs)/h over a mean follow-up period of 25 months. Expected death rates are based on a 16 variable logistic regression model.

infarction (before the qualifying myocardial infarction), the age of the patient and the presence of congestive heart failure during hospitalization for the qualifying infarction. A history of angina diagnosed by the Rose questionnaire was associated with two of the three definitions of ventricular ectopic activity and race with one definition. There was no relation between ectopic activity and the site (anterior, inferior, Q versus non-Q) of the infarction, serum potassium or heart rate.

Relation of ventricular ectopic activity to mortality (Fig. 1, Table 3). In a multivariate logistic regression analysis, ventricular ectopic activity, defined as the number of ventricular premature beats/h, was a significant predictor of total mortality (t = 2.47) independent of other variables that may reflect left ventricular impairment [serum lactate dehydrogenase (LDH) level, cardiothoracic ratio, congestive heart failure, prior myocardial infarction], traditional risk factors (age, smoking, cholesterol, diabetes mellitus), and other characteristics (ST depression, complications during hospitalization) associated with mortality in this cohort. In addition, a significant independent contribution of ventricular arrhythmia in predicting mortality was observed when alternate continuous or categorical descriptors of ventricular ectopic activity were used (Table 3). Figure 1 describes the univariate increasing risk of mortality with increasing number of ventricular premature beats/h and the goodness of fit of the 16 variable logistic model. The presence of more than 0 ventricular premature beats/h, the presence of pairs or ventricular tachycardia and the presence of ≥10 ventricular premature beats/h and [pair or ventricular tachycardia] and multiform complexes showed trends that did not reach nominal statistical significance. The remaining eight definitions showed statistically significant (adjusted t value ranging from 2.42 to 4.26) independent associations with total mortality when used alone in the multivariate model. When atherosclerotic sudden death or atherosclerotic nonsudden death was considered, the level of significance of the associations was generally lower, perhaps as a result of the smaller number of end points.

The relation between ventricular ectopic activity and total mortality, atherosclerotic sudden death and atherosclerotic nonsudden death persisted when only patients with a Q/QS

Table 3. Coefficients for Holter Characteristics from 33 Multivariate* Logistic Regressions: for Each End Point, 11 Regressions Were Run, 1 for Each Holter Characteristic

	Total Mortality (16 variable models; % of deaths = 129/1,308 = 9.9%)			Atherosclerotic Sudden Death (1 hour) (11 variable models; % of deaths = 68/1,528 = 4.5%)			Atherosclerotic Nonsudden Death (12 variable models; % of deaths = 51/1,292 = 3.9%)		
Holter Characteristic Used in Model	Adjusted t Value	Adjusted Odds Ratio	Logistic Coefficient	Adjusted t Value	Adjusted Odds Ratio	Logistic Coefficient	Adjusted t Value	Adjusted Odds Ratio	Logistic Coefficient
Continuous variables									
VPB	*2.47*	1.003‡	0.00296	−0.13	0.999	−0.00014	0.32	1.00	0.00038
LNVPB	*2.85*	1.23	0.20886	1.62	1.15	0.13933	1.77	1.19	0.17663
PAIR	*2.63*	1.18	0.16898	−0.56	0.99	−0.01342	−0.15	1.00	−0.00248
VT	*4.26*†	3.52	1.25838	−0.47	0.89	−0.11490	*2.02*†	2.46	0.90090
Categoric variables									
VPB0	1.24	1.53	0.42623	1.10	1.71	0.53495	1.49	2.51	0.92121
VPB10	*3.14*	2.23	0.80222	1.88	1.81	0.59235	*2.24*	2.25	0.81150
PAIRVT	1.60	1.46	0.37563	1.01	1.34	0.29596	0.98	1.39	0.32979
OR	*3.38*	2.07	0.72683	1.90	1.68	0.52026	*2.46*	2.13	0.75778
MULT	*2.42*	1.67	0.51184	*3.22*	2.43	0.88685	0.63	1.21	0.19310
ANDAND	0.69	1.27	0.23812	0.98	1.47	0.38334	−0.18	0.91	−0.09837
OROR	*3.37*	2.02	0.70458	*2.84*	2.21	0.79517	1.63	1.65	0.49808

*See Appendix for variables controlled in mutivariate analyses. †Walker-Duncan model would not converge. This was calculated from Truett-Cornfield estimates. ‡This means that there is a 0.3% increase in risk for every increase of one ventricular premature beat/h. ANDAND = VPB ≥10/h and (VT event or pair) and multiform complexes (0 = no; 1 = yes); LNVPB = ln (VPB/h + 0.5); MULT = multiform VPB present (0 = no; 1 = yes); OR = VPB ≥10/h or VT event or pairs (0 = no; 1 = yes); OROR = VPB ≥10/h or (VT event or pairs) or multiform complexes; PAIR = VPB pairs/h; PAIRVT = VT event or VPB pair present (0 = no; 1 = yes); VPB = ventricular premature beats/h; VPBO = mean VPB/h>0 (0 = no; 1 = yes); VPB10 = mean VPB/h ≥10 (0 = no; 1 = yes); VT = ventricular tachycardia events/h. Values in italic denote a t value >1.96.

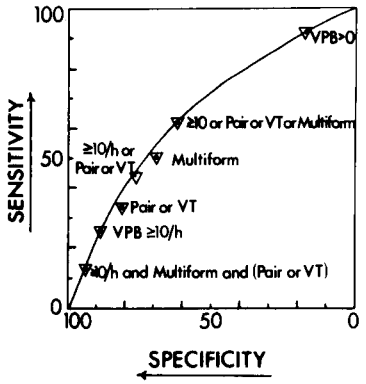

Figure 2. Reciprocal relation between sensitivity and specificity of seven definitions of ventricular arrhythmias in predicting mortality rate of survivors of acute myocardial infarction. 1 = VPB > 0; 2 = VPB ≥ 10/h; 3 = VPB pair or VT; 4 = VPB ≥ 10/h; 5 = multiform complexes; 6 = VPB ≥ 10/h and VPB (pair or VT) and multiform complexes; 7 = VPB ≥ 10/h or VPB pair or VT or multiform complexes. VPB = ventricular premature beats; VT = ventricular tachycardia.

wave infarction were considered (odds ratios 2.39 to 2.91, t = 2.37 to 4.57). In the BHAT placebo group, the mortality rate in patients with a Q/QS wave infarction was not significantly different from that in patients with a non-Q wave infarction (41). A significant association of ventricular ectopic activity with nonfatal infarction was not observed.

The usefulness of different definitions of ventricular arrhythmias (Fig. 2, Tables 4 and 5). Most definitions of ventricular arrhythmia were multivariately associated with mortality. Therefore, a different analysis may be useful in selecting a definition appropriate for a given clinical problem.

Rates for total mortality, atherosclerotic sudden death and atherosclerotic nonsudden death cross-tabulated by the presence or absence of the seven categorical definitions of ventricular ectopic activity are presented in Table 4. Again, in this univariate analysis, all definitions showed a significant association with all three mortality classifications. The odds ratios were also similar (2.18 to 2.69). However, the sensitivity (percent of patients who died and also had ectopic activity by a given definition at baseline study) and specificity (percent of patients who did not die and did not have arrhythmia by that definition) of the different definitions in predicting future mortality were markedly different (Table 5). These are presented pictorially as a "receiving operator characteristic curve" in Figure 2 (42). Definitions with high

Table 4. Event Rates by Holter Variable

		Total Mortality			Atherosclerotic Sudden Death (<1 hour)			Atherosclerotic Nonsudden Death		
	Total No. of Patients	Death Rate (%)	Odds Ratio	Z of Diff.	Death Rate (%)	Odds Ratio	Z of Diff.	Death Rate (%)	Odds Ratio	Z of Diff.
Overall	1,640	9.9	—	—	4.6	—	—	4.0	—	—
VPB >0/24 h										
Yes	1,380	10.9	2.32	2.90	5.1	2.26	1.95	4.5	3.01	2.22
No	260	5.0			2.3			1.5		
VPB ≥10/h										
Yes	211	19.9	2.69	5.18	9.0	2.38	3.24	8.1	2.47	3.19
No	1,429	8.5			4.0			3.4		
VPB pair or VT present										
Yes	327	16.5	2.18	4.44	8.0	2.18	3.19	6.7	2.08	2.78
No	1,313	8.3			3.8			3.4		
VPB ≥10/h or (VPB pair or VT)										
Yes	418	17.2	2.59	5.77	7.9	2.35	3.67	7.2	2.55	3.80
No	1,222	7.4			3.5			2.9		
Multiform present										
Yes	538	15.2	2.27	5.02	8.7	3.54	5.52	5.6	1.75	2.23
No	1,102	7.4			2.6			3.3		
VPB ≥10/h and (pair or VT) and multiform complexes										
Yes	112	19.6	2.40	3.56	10.7	2.75	3.17	7.1	1.95	1.74
No	1,528	9.2			4.2			3.8		
VPB ≥10/h or (pair or VT) or multiform complexes										
Yes	666	15.2	2.63	5.85	7.7	3.15	4.82	5.9	2.18	3.12
No	974	6.4			2.6			2.8		

Table 5. Sensitivity and Specificity of Seven Categorical Definitions of Ventricular Arrhythmia in Predicting Mortality

Arrhythmia Definition	No. of Deaths (a)	No. With Arrhythmia (b)	Sensitivity (c = b/a)	No. Alive (d)	No. Without Arrhythmia (e)	Specificity (f = e/d)
Total Mortality						
VPB >0/24 h	163	150	0.920	1,477	247	0.167
VPB ≥10/h	163	42	0.258	1,477	1,308	0.886
VPB pair or VT present	163	54	0.331	1,477	1,204	0.815
VPB ≥10/h or VPB pair or VT	163	72	0.442	1,477	1,131	0.766
Multiform present	163	82	0.503	1,477	1,021	0.691
VPB ≥10/h and pair or VT and multiform	163	22	0.135	1,477	1,387	0.939
VPB ≥10/h or pair or VT or multiform	163	101	0.620	1,477	912	0.617
Atherosclerotic Sudden Death (<1 hour)						
VPB >0/24 h	76	70	0.921	1,564	254	0.162
VPB ≥10/h	76	19	0.250	1,564	1,372	0.877
VPB pair or VT present	76	26	0.342	1,564	1,263	0.808
VPB ≥10/h or VPB pair or VT	76	33	0.434	1,564	1,179	0.754
Multiform present	76	47	0.618	1,564	1,073	0.686
VPB ≥10/h and pair or VT and multiform	76	12	0.158	1,564	1,464	0.936
VPB ≥10/h or pair or VT or multiform	76	51	0.671	1,564	949	0.607
Nonsudden Atherosclerotic Death						
VPB >0/24 h	66	62	0.939	1,574	256	0.163
VPB ≥10/h	66	17	0.258	1,574	1,380	0.877
VPB pair or VT present	66	22	0.333	1,574	1,269	0.806
VPB ≥10/h or VPB pair or VT	66	30	0.455	1,574	1,186	0.753
Multiform present	66	30	0.455	1,574	1,066	0.677
VPB ≥10/h and pair or VT and multiform	66	8	0.121	1,574	1,470	0.934
VPB ≥10/h or pair or VT or multiform	66	39	0.591	1,574	947	0.602

Abbreviations as in Table 3.

sensitivity and low specificity (for example, ventricular premature beats >0/h) or vice versa (for example, ventricular premature beats ≥10/h and pairs or ventricular tachycardia and multiform complexes) may be identified. The inverse relation of sensitivity and specificity is evident. Using two additional categoric ventricular ectopic activity definitions (presence of ventricular tachycardia; presence of ≥10 ventricular premature beats/h and [pairs or ventricular tachycardia]) gave similar results. For ventricular tachycardia, sensitivity was 0.17 and specificity was 0.93; for the presence of both greater than 10 ventricular premature beats/h and pairs or ventricular tachycardia, sensitivity was 0.147 and specificity was 0.935.

Prediction of mortality in patient subsets defined by clinical variables (Fig. 3, Table 6). Good stratification of risk was obtained with the use of three clinical characteristics [history of prior myocardial infarction, cardiomegaly (that is, cardiothoracic ratio >0.5) and ST depression on the rest electrocardiogram]. Four subsets of patients with mortality rates ranging from 4.7 to 35.5% were defined by the presence of none, one, two or three characteristics. The presence of ventricular ectopic activity increased the risk in all subsets. The risk ratios for patients with and without arrhythmia and the level of significance of the differences in mortality were higher in the low risk and numerically larger strata. For the purposes of this analysis, ectopic activity was de-

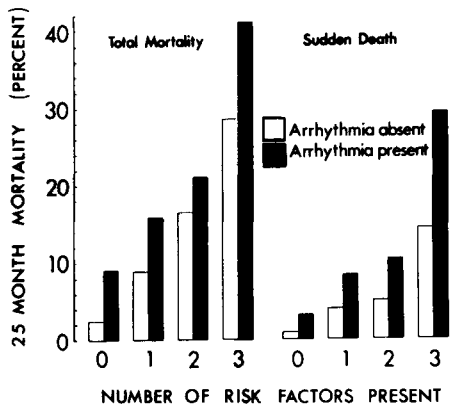

Figure 3. Total 25 month mortality and sudden death mortality according to the number of "risk factors" [prior myocardial infarction, cardiothoracic ratio >0.5, ST depression on rest electrocardiogram and the presence or absence of ventricular ectopic activity (≥10 ventricular premature beats/h or pairs or ventricular tachycardia or multiform complexes)].

fined as the presence of ≥10 ventricular premature beats/h or pairs or ventricular tachycardia or multiform complexes.

Discussion

Ventricular ectopic activity in survivors of acute myocardial infarction. The prevalence of the different forms of ventricular ectopic activity observed in this study was similar to that previously reported by some investigators (11,26), but lower than that reported by others (10,16,18,19,30,33). Discrepancies in the prevalence of ectopic activity among different studies may be due to different characteristics of the study groups under consideration, different recording methodology, exclusion criteria, the use of antiarrhythmic agents during ambulatory ECG and other factors. In this study, antiarrhythmic agents were used by 291 patients (17.7%) and certain types of high risk patients, including those with uncontrolled congestive heart failure, were excluded. The association of left ventricular dysfunction with ventricular arrhythmias and mortality may explain why both ectopic activity and mortality were higher in other series of survivors of acute myocardial infarction (18,19,32–34).

This study confirms previous findings (11,33,43–45) of a strong relation between ventricular ectopic activity and left ventricular dysfunction. Thus, the presence of congestive heart failure and history of myocardial infarction before the qualifying infarction, two factors related to left ventricular dysfunction, were associated with ectopic activity in this study. An independent effect of age on ectopic activity was also observed in this cohort, and has been previously reported (46–48) in patients with and without cardiac disease. A relation to the site of infarction (transmural versus subendocardial, anterior versus inferior) was not seen (43).

Table 6. Total Mortality and Sudden Death Mortality in Four Subsets of Patients in the Presence and Absence of Ventricular Arrhythmia

No. of Risk Factors Present*	Total No. in Group	% With Arrhythmia	All Deaths								Sudden Death							
			Overall Death Rate/100	VA present			VA absent			Z of Difference Between Rates	Overall Death Rate/100	VA Present			VA Absent			Z of Difference Between Rates
				Total No.	No. Dead	Death Rate/100	Total No.	No. Dead	Death Rate/100	Relative Risk		Total No.	No. Dead	Death Rate/100	Total No.	No. Dead	Death Rate/100	Relative Risk	
3	31	54.8	35.5	17	7	41.2	14	4	28.6	1.44	0.73	22.6	17	5	29.4	14	2	14.3	2.06	1.00
2	205	55.6	19.0	114	24	21.1	91	15	16.5	1.28	0.83	8.8	114	13	11.4	91	5	5.5	2.08	1.49
1	547	39.3	11.5	215	34	15.8	332	29	8.7	1.81	2.53	5.7	215	18	8.4	332	13	3.9	2.14	2.20
0	591	35.4	4.7	209	19	9.1	382	9	2.4	3.86	3.68	1.7	209	7	3.3	382	3	0.8	4.26	2.31
Total	1374	40.4	10.3	555	84	15.1	819	57	7.0	2.17	4.90	4.8	555	43	7.7	819	23	2.8	2.76	4.20

*Risk factors = prior myocardial infarction, cardiothoracic ratio <0.5, ST depression; VA = ventricular arrhythmia (VPB ≥10/h or pair or VT or multiform beats).

Relation of ventricular ectopic activity to mortality of survivors of acute myocardial infarction. This relation has been the subject of many reports. Although some smaller studies (34,43,49,50) did not show such a relation, the majority of reports (15,16,19,24,25,29,30,32,33) show that patients with ectopic activity, especially frequent or complex, have higher mortality rates. There is still some question as to whether the relation between increased mortality and ectopic activity is independent of other factors influencing prognosis, such as left ventricular dysfunction.

Because left ventricular dysfunction is both a major predictor of mortality and an important determinant of ventricular ectopic activity, it has been postulated that arrhythmias do not independently contribute to the risk, but are merely markers of severe disease (myocardial damage). In this study, multiple logistic regression identified ectopic activity as an independent predictor of mortality after numerous other variables, including factors indirectly reflecting or associated with left ventricular dysfunction (prior myocardial infarction, cardiothoracic ratio, history of congestive heart failure, elevated LDH or use of digitalis), were taken into consideration (Fig. 1).

Contrary to a recent report (35) of 586 patients, we found that ventricular ectopic activity was a significant predictor of risk in patients with a Q/QS wave infarction. This difference may be a result of patient selection, other methodologic differences (for example, ambulatory ECG was not a required part of the protocol, different definitions of significant Q waves) or chance.

Risk stratification based on clinical variables and ventricular ectopic activity. Cardiac catheterization, estimation of ejection fraction using radionuclides, exercise testing and invasive electrophysiologic studies have been used for risk stratification of survivors of acute myocardial infarction (51–59). These expensive techniques have significant economic impact when applied to all patients with a common disorder such as myocardial infarction. The present study shows that stratification of patients according to risk of future mortality may be done using easily obtainable and inexpensive clinical criteria such as the history of a prior myocardial infarction, ST depression on the rest ECG and cardiomegaly on chest X-ray film. These factors, which were also associated with increased mortality in previous studies (12,21,45,49,60–63), resulted in a 7.5-fold risk differential with the 25 month mortality rate varying from 4.7% with none of the three factors present to 35.5% when all three factors were present (Fig. 3, Table 6). This is either similar or better than the stratification reported by other workers (51–59) using radionuclide imaging, exercise testing or electrophysiologic study.

Ambulatory ECG is frequently employed in patients recovering from acute myocardial infarction to estimate the risk of future mortality. Because the risk is high mainly in patients who have both left ventricular dysfunction and frequent or complex ventricular ectopic activity, physicians tend to employ ambulatory ECG only in patients who have significant left ventricular dysfunction, multiple infarctions or other factors associated with high risk. In this study, ventricular ectopic activity increased the risk in all risk strata, allowing identification of eight subsets with a 17-fold risk range. For sudden cardiac death, the mortality rate varied from 0.8 to 29.4%. This risk ratio of 38 (highest to lowest stratum) is almost 3.5 times higher than that found by Mukharji et al. (33), who classified Multicenter Investigation of the Limitation of Infarct Size (MILIS) patients by ejection fraction and ventricular ectopic activity. In the present study of the BHAT placebo group, although the absolute increment of risk imposed by ectopic activity was similar in the four mortality strata defined by the history of prior myocardial infarction, ST depression and cardiomegaly, the risk ratio was higher in the low mortality subset that included the largest number of subjects. In this subset (patients without ST depression, cardiomegaly or prior infarction), ectopic activity almost quadrupled the risk. This suggests that if ambulatory ECG is used for risk stratification, its use should not be confined only to high risk patients.

Association of ventricular ectopic activity with both sudden and nonsudden coronary death. A probable mechanism by which ectopic activity may be associated with increased mortality independently of other factors is precipitation of ventricular fibrillation (for example, R on T ventricular premature beats may precipitate ventricular tachycardia and fibrillation). Nonsustained asymptomatic ectopic activity may also be a marker of "electrical instability" or tendency of the ventricles to fibrillate. From these considerations, one would expect the mortality risk ratios to be higher for sudden death than for nonsudden coronary death. This pattern was not consistently observed in this study. In other studies (24), ventricular arrhythmias, especially repetitive forms, were found to be the best predictor for sudden cardiac death, whereas congestive heart failure was a stronger predictor of nonsudden death. Variability in the definition of sudden cardiac death as to the time interval from the onset of symptoms (for example, instantaneous or 1 hour) or as to circumstances (for example, exclusion of patients who had clinical or pathologic evidence of acute myocardial infarction even if they died within 1 hour of the onset of symptoms) may be responsible for the different results, in addition to the differences between studies mentioned earlier (19,33). The lack of preferential association of ectopic activity with sudden rather than nonsudden death may imply that asymptomatic ectopic activity is a marker of electrical instability that increases the risk of death in all patients with coronary artery disease (both in the presence and absence of clinically recognized ischemic events such as myocardial infarction).

Value of different definitions of ventricular ectopic activity in risk stratification. Much discussion has been devoted to whether frequency or complexity of ectopic ac-

tivity is the stronger predictor of mortality in survivors of acute myocardial infarction. The data from BHAT combined with those from previous reports indicate that both frequency and complexity are important. In BHAT, low frequency of ventricular premature beats (<10/h) or absence of repetitive ventricular premature beats was associated with lower (8.5 and 8.3%, respectively) mortality than either high frequency (≥10/h) of ventricular premature beats (mortality 19.9%) or presence of complex forms (pairs or ventricular tachycardia, 16.5% mortality). Among the different types of complexity, the risk ratios for the presence of repetitive forms and multiform ventricular premature beats were similar. In some previous studies (19,24,25), repetitive forms were found to increase risk to a higher degree than the presence of other types of complexity, while in other studies (33), a ventricular premature beat frequency ≥10/h was a stronger predictor.

Because the great majority of survivors of acute myocardial infarction manifest some ventricular ectopic activity on 24 hour ambulatory ECG, the mere presence of ventricular premature beats is not useful in identifying high risk subgroups. More malignant forms (for example, ≥10 ventricular premature beats/h, multiform complexes and pairs or ventricular tachycardia) identify subgroups at high risk, but occur in only a small percent (6.7%) of patients and in only a small percent (13.5%) of patients who will die.

Selection of an appropriate arrhythmia definition. Physicians facing the decision of whether or not to intervene (for example, treat with antiarrhythmic agents) prefer to use categoric definitions of ventricular ectopic activity. All such definitions applied in BHAT were associated with increased mortality with similar odds ratios (ranging from 2.18 to 2.63). Therefore, in this respect, the definitions of ectopic activity are similar (that is, univariably, the odds of dying for a patient with one or more ventricular premature beats/24 h were 2.32 times higher than the odds for a patient without any ventricular premature beats/24 h; or the odds of dying for a patient with paired beats or ventricular tachycardia were 2.18 times higher than the odds for a patient without pairs or ventricular tachycardia) (Table 4). On multivariate analysis, the odds of dying for a patient with one or more ventricular premature beats/24 h were 1.53 times higher than the odds for a patient without any ventricular premature beats/24 h, and the odds of dying for a patient with pairs or ventricular tachycardia were 2.07 times higher than the odds for a patient without pairs or ventricular tachycardia (Table 3).

A more useful approach in deciding on the appropriate

Appendix

Patient Characteristics at Entry Used as Independent Variables in the Multiple Logistic Regression Models

Patient Characteristics	Total Mortality	Atherosclerotic Sudden Death	Atherosclerotic Nonsudden Death
Age (yr)*	X	X	X
Employed*	X		
Current cigarette smoker*	X	X	X
Prior myocardial infarction*	X	X	
Diastolic blood pressure (mm Hg)	X		
Systolic blood pressure (mm Hg)		X	
Heart rate (beats/min)		X	X
Hematocrit (%)	X		
Serum cholesterol (mg/dl)			X
Elevated LDH*	X	X	X
Anteriorly located infarction (from ECG)*		X	
ST depression (from ECG)*	X	X	
Major left ventricular hypertrophy (from ECG)*			X
Cardiothoracic ratio (from X-ray film)	X		X
Experienced complications during hospitalization*	X		
History of congestive heart failure*	X	X	
History of diabetes*	X		X
Beta-blocker use before BHAT myocardial infarction*	X		X
Antiplatelet use at entry	X		
Digitalis use at entry*			X
Antiarrhythmic drug use at entry*	X	X	X
(Holter characteristic from 24 hour Holter)*	X	X	X

0 = No, 1 = Yes. ECG = electrocardiogram; LDH = lactic dehydrogenase.

definition of ventricular ectopic activity for a given clinical or research setting is to use information included in Tables 4 and 5. When only a subset of patients with high or low mortality is to be identified, the data presented in Table 4 are useful. For example, a person with ≥10 ventricular premature beats/hour and multiform complexes and pairs or ventricular tachycardia has a mortality rate approximately four times higher (19.6% in 25 months) than a person without any ventricular premature beats in 24 hours (5.0%). Treatment of only the patients with this definition of ventricular arrhythmia would afford a potential benefit only to 13.4% (22 of 163) of the patients who eventually die and would not benefit the majority of patients at risk. Therefore, it is important to consider not only the risk of a given subset of patients with a given definition of ectopic activity, but also the sensitivity of each categoric definition of arrhythmia in identifying patients who died and the specificity of the definition in identifying patients who did not die during follow-up (Fig. 2, Table 5). By using this type of analysis, it becomes easier to tailor the definition of ectopic activity to the proposed intervention.

When an intervention with a low level of adverse effects is contemplated, a definition with a high sensitivity (and low specificity) can be employed to offer the benefit to most patients at risk of dying. The large number of patients not at risk who will be treated because of the low specificity of the definition will not suffer severe adverse reactions. On the other hand, when interventions that are expensive or carry significant risk or suffering are considered, a definition with a high specificity can be chosen to avoid treating a large number of persons not at increased risk of dying with a potentially toxic agent. In this case, however, the percent of persons that will be treated will be low.

Although ventricular ectopic activity is associated with an increased mortality in survivors of acute myocardial infarction and although it most probably contributes to the risk independently of other factors, there is no evidence to date that treatment of the arrhythmia reduces the risk. Published studies (64) of antiarrhythmic therapy in acute myocardial infarction have not proved a beneficial effect. However, these studies were small (low statistical power), the particular antiarrhythmic agents tested may not have been effective, single drugs in fixed doses were used and, in some studies, ambulatory ECG to define the risk and the efficacy of treatment was not employed. A pilot study on this issue has been completed and a large study is now in progress (65).

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